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EXAMINER

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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Paper No. 02022004

Application Number: 08/571,802
Filing Date: December 13, 1995
Appellant(s): ISHII, DOUGLAS N.

Janelle D. Waack
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 03 December 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) *Related Appeals and Interferences*

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

(3) *Status of Claims*

The statement of the status of the claims contained in the brief is correct.

(4) *Status of Amendments After Final*

The appellant's statement of the status of amendments after final rejection contained in the brief is incorrect.

No amendment after final has been filed.

(5) *Summary of Invention*

The summary of invention contained in the brief is correct.

(6) *Issues*

The appellant's statement of the issues in the brief is correct.

(7) *Grouping of Claims*

Appellant's brief includes a statement that claims 24-72 do stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) *Claims Appealed*

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5093317 LEWIS et al. 3-1992

Hensyc W.R. Stedman's Medical Dictionary, 25th edition, 1990, p. 1626.

Berkow et al. (1982) The Merck Manual of Diagnosis and Therapy. 14th Edition. Merck & Co., Inc., Rahway, N.J., pp.1324-1339.

Rieger et al. Glossary of Genetics, 1991, pp. 16-17.

Jackowski (1995) British Journal of Neurosurgery 9: 303-317.

Barnes (1987) Science 235: 1574-1577.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The rejection of claims 24-71 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of the arguments set forth by the appellant.

Claims 24-71 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description and new matter rejection.

Claims 24-71 recite the terms "IGF-I" and "IGF-II" which encompass proteins which are allelic variants given the definition of "IGF-I" and "IGF-II" on pages 5-6 of the specification. Thus, the claims encompass a subgenus of "naturally occurring allelic variants" which is not disclosed in the specification. The ordinary meaning of the term allele is one of two or more alternate forms of a gene occupying the same locus in a particular chromosome or linkage structure and differing from other alleles of the locus at one or more mutation sites (see Rieger et al., *Glossary of Genetics* (1991), pages 16-17). However, the specification only discloses by name one species each of IGF-I and IGF-II in the working example. The general knowledge in the art concerning alleles does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is such that they are variant structures and in the present state of the art the structure of one does not provide guidance to the structure of others. The common attributes of the genus are not described. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claim. *University of California v. Eli Lilly and Co.* (CAFC) 43 USPQ2d 1398 held that a generic claim to human or mammalian when only the rat protein sequence was disclosed did not have written description in the specification.

Claims 24-71 recite the terms "parenteral nonintracranial administration" which are not disclosed in the specification. The original claims recite parenteral administration that is generic and does not provide support for the subgeneric limitation

claimed. The specification does not provide written descriptive support for the subgenus encompassing administration by all means other than intracranial.

Claims 24-71 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of parenteral administration of species of IGF-I, IGF-II, or a combination of both IGF-I and II for the treatment of locus ceruleus noradrenergic neurons ablation by 6-hydroxydopamine, does not reasonably provide the full scope of enablement for parenteral administration of IGF-I or IGF-II, for traumatic injury of the central nervous system (CNS) or spinal cord and treating stroke. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the reasons set forth in the past office actions.

The terms "traumatic injury to the central nervous system" encompass a physical or mental injury to the central nervous system (see Stedman's Medical Dictionary(U)). Thus, claims 24-33 encompass any physical or mental injury to the CNS. The term "stroke" encompasses both ischemic or hemorrhagic lesions. Thus, claims 34-45 encompass treatment for all types of stroke. The terms "traumatic brain injury" encompass a physical or mental injury to the brain (see Stedman's Medical Dictionary(U)). Thus, claims 40-45 encompass any physical or mental injury to the brain. Claims 57-71 recite and encompass the term "injury to the central nervous system" which encompasses any physical or mental injury to the central nervous system. However, the specification fails to teach treating the generic injury or stroke.

The claims generic encompass dysfunction in the CNS from molecular, cellular, physiological, neural network, to behavior in normal and disordered state and the state of the art at the time of the invention provides no reference to indicate that administering IGF-I or -II will treat all such injuries in the CNS or spinal cord. Just a few examples of such injury includes schizophrenia, depression, spinal cord transection, ion channel modulation, or memory which the state of the art is silent with respect to treatment with IGF-I or II. Baringa (A34) provides the state of the art after the time of the invention where treatments of nervous system diseases with neurotrophic factors are unpredictable and that treatment of any one disease is not predictive of another. Baringa further indicates that although treating peripheral neuropathy may be more promising, even with sensory peripheral neuropathy, there is a difference between diabetic neuropathy and cancer chemotherapy induced neuropathy (A34, page 774, left column). Thus, the treatment of a nervous system disease is an unpredictable art where one model of treatment for neuropathy is not predictive of the another model of treatment. Although the specification provides working examples of IGF-II mRNA changes in the streptozotocin induced diabetic rat brain by administration of IGF-I (pages 11-12) and working examples of IGF-II administration for treatment of 6-hydroxydopamine (6OHDA) induced noradrenergic locus ceruleus ablation by measuring limb withdrawal reflex, such examples are not predictive of effecting any changes in CNS or spinal cord, or treating any disorders or diseases in the brain or spinal cord, because the state of the art indicates that any one model of treatment for a disease is not predictive of the another model of treatment. Further indication that

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treatment of neurological disease is an unpredictable art is indicated by Jackowski(R) who teaches that neurons do not regenerate the CNS because CNS environment is non-supportive or actively inhibitory to neuronal regeneration (reference R is cited as being of interest to applicant's specification, page 305, right column, bottom paragraph). Working example in the specification of IGF-II administration for treatment of 6-hydroxydopamine (6OHDA) induced noradrenergic locus ceruleus ablation by measuring limb withdrawal reflex is not predictive of treating any disorders or diseases in the brain or spinal cord, because the state of the art indicates that CNS is inhibitory to neuronal regeneration and regeneration is necessary for treatment of CNS diseases. Shepherd(S) disclose the state of the art by teaching how the CNS is categorized and the noradrenergic neurons of the locus ceruleus is but a small region in the whole CNS and the noradrenergic neurons of the locus ceruleus are different from other regions of the brain such as the dopaminergic neurons of the striatum(reference S is cited as being of interest to applicant's specification, page 499, figure 24.9 and section "Norepinephrine"; page 501, figure 24.10 and left column). Since the treatment of CNS is an unpredictable art because the CNS is inhibitory to regeneration, the working example for treatment of noradrenergic locus ceruleus is not predictive of any other regions of the brain nor any other types of neurons. Finally, the treatment of CNS injury encompasses treatment of AIDS dementia which is an unpredictable art because the state of the art at the time of the invention does not indicate any reference that administering IGF-I or -II will be effective in treatment of AIDS dementia. Barnes(T) teaches the state of the art at the time of the invention regarding how AIDS virus injures

the nervous system and indicates uncertainty and controversy about the mechanism of the injury (S, page 1574, left column, top paragraph). Barne's discussion concerning AIDS dementia is limited to the etiology and no discussion concerning treatment with IGF-I or II is provided (S, page 1574, left column, top paragraph). The working examples are not predictive of treating AIDS dementia because the specification fails to provide a model for AIDS dementia which could be used predict the effect of treatment by administering IGF-I or -II. Without such guidance, the determination of IGF-I or -II effect on treating AIDS dementia requires empirical experimentation and are not predictive of treating AIDS dementia. Thus without further guidance, it would require undue experimentation to determine all the changes effected in the CNS or spinal cord by administering IGF- or IGF-II as well as all the disorders of the brain or spinal cord including AIDS dementia. Furthermore, the specification fails to teach the treatment for the full scope of stroke diseases. The state of the art is silent with respect to using IGF to treat stroke (see Berkow et al.(V)). The treatments are related to using anticoagulants or treating atherosclerosis or hypertension, but not using IGF. Furthermore, the specification fails to make a nexus from the model of using IGF-I and II for the treatment of locus ceruleus noradrenergic neurons ablation by 6-hydroxydopamine to treating stroke or Parkinson disease. Without such guidance, the determination of IGF-I or -II effect on treating the full scope of stroke diseases is unpredictable because strokes can occur in other regions of the brain and there is no relationship between the noradrenergic neuronal ablation by 6-hydroxydopamine of

locus ceruleus. Thus without further guidance, it would require undue experimentation to treat stroke by administering IGF- or IGF-II.

Claims 24-71 are rejected under 35 U.S.C. 102(e) as being anticipated by Lewis et al.(A1).

The terms "traumatic injury to the central nervous system" or "traumatic brain injury" encompass a physical or mental injury to the central nervous system or brain. Lewis et al. teach a method of treating injury and stroke (column 4, lines 1-22). Lewis et al. teach a method of parenteral administration of IGF-I or IGF-II with specific dosage ranges of 1ug/kg/day to 1 g/kg/day as well as ranges 0.01 mg/kg/day to 100mg/kg/day (column 10, lines 3-22). Furthermore, IGF I and II inherently cross the blood brain barrier.

Claims 46-56 encompass a method of treating locus ceruleus neurons with IGFs. Lewis et al. teach method of treatment for diseases such as Alzheimer's disease, stroke, epilepsy, amyotrophic lateral sclerosis, or Parkinson's disease by administering an effective amount of IGF I or IGF II or a combination thereof. Diseases such as stroke and Parkinson's disease affect the locus ceruleus neurons. Thus, the treatment by the parenteral administration of IGF I or IGF II to treat these diseases comprise a nonintracranial administration of an IGF in an amount to effective to treat the locus ceruleus neurons.

Claims 57-67 encompass a method of treating the central nervous system. Lewis et al. teach method of treatment for diseases such as Alzheimer's disease,

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stroke, epilepsy, amyotrophic lateral sclerosis, or Parkinson's disease by administering an effective amount of IGF I or IGF II or a combination thereof. These diseases are injury which affect the central nervous system.

Claims 68-71 are dependent claims that encompass a method of treating with IGF damage to locus ceruleus associated with Parkinson's disease. Parkinson's disease is associated with damage to the locus ceruleus neurons. Thus, the treatment by the parenteral administration of IGF I or IGF II to treat Parkinson's disease comprise a nonintracranial administration of an IGF in an amount effective to treat the disease, wherein the locus ceruleus is damaged.

(11) Response to Argument

Claims 24-71 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description and new matter rejection.

Appellants argue on pages 3-4 that IGF claim limitation does not include derivatives of IGF's including fragments of IGF's, analogs of IGF's, or analogs of fragments of IGF's because of the definitions of IGF-I and IGF-II in the specification on page 5. However, the specification on page 5, lines 21-25 specifically recite that "IGF-I also encompasses ... IGF molecules with substantial sequence homology to human and animal IGF-I that bind to type I IGF receptors." Thus, the claims encompass and

claim a subgenus of “naturally occurring allelic variants” which is not disclosed in the specification. The ordinary meaning of the term allele is one of two or more alternate forms of a gene occupying the same locus in a particular chromosome or linkage structure and differing from other alleles of the locus at one or more mutation sites (see Rieger et al., *Glossary of Genetics* (1991), pages 16-17). However, the specification only discloses by name one species each of IGF-I and IGF-II in the working example. The general knowledge in the art concerning alleles does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is such that they are variant structures and in the present state of the art the structure of one does not provide guidance for the structure of others. Appellant does not describe a representative number of the claimed genus, and the common attributes of the genus are not described. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claim. *University of California v. Eli Lilly and Co. (CAFC) 43 USPQ2d 1398* held that a generic claim to human or mammalian when only the rat protein sequence was disclosed did not have written description in the specification.

Appellants discuss on page 5 of the Brief a newly submitted reference “Concise Encyclopedia Biochemistry” which has not been considered because it does not comply with 37 CFR 1.195.

Appellants on page 5 of the Brief argue that *Eli Lilly* does not apply because the specification describes and defines IGF’s and persons of skill in the art understand the

functional and structural characteristics of IGFs. However, the issue is whether applicant's definition in the specification on page 5, lines 21-25 when it specifically recites that "IGF-I also encompasses ... IGF molecules with substantial sequence homology to human and animal IGF-I that bind to type I IGF receptors" encompasses generically IGF molecules other than the species disclosed in the specification. The definition on page 5 encompasses a generic class of IGF-I while the specification discloses only the species of IGF-1. *Eli Lilly* does prohibit claiming a genus when the genus of molecules cannot be envisioned from the disclosed species. Appellants' citation of *Amgen Inc. v. Hoescht Marion Roussel, Inc.* does not overcome the rejection because unlike *Amgen* the inability to envision the generic sequences of IGF-I or IGF-II when only the species are provided in this application is pertinent to *Eli Lilly*.

Appellants argue on page 4 of the Brief that the rejection is not correct regarding the new matter rejection of claims 24-71 which claims now encompass the terms "IGF-I consists essentially of an amino acid sequence of a naturally occurring IGF-I" and "IGF-II consists essentially of an amino acid sequence of a naturally occurring IGF-II" are not persuasive because the claim limitations are not disclosed in the specification,. Pages 5-6 of the specification define the terms "IGF-I" and "IGF-II" that are generic and does not provide support for the subgeneric limitations claimed. Appellants argue that "naturally occurring" IGFs is not new matter because a persons skilled in the art would understand that functional derivatives of IGF's are not naturally occurring IGF's. However, the specification on page 5, lines 21-25 specifically recite that "IGF-I also encompasses ... IGF molecules with substantial sequence homology to human and

animal IGF-I that bind to type I IGF receptors." Thus, claims encompass "IGF-I" and "IGF-II" which are generic and does not provide support for the subgeneric limitations claimed. Appellants argue that the claims only encompass all naturally occurring forms of IGFs. However, the definition in the specification is generic to the subgeneric claim limitation of "naturally occurring" and the specification does not disclose "naturally occurring." Furthermore, the specification does not disclose what is non-naturally occurring or not naturally occurring which is necessary to disclose the IGFs that are naturally occurring.

Appellants argue in the page 6 of the Brief that the term "parenteral nonintracranial administration" is not new matter. Appellants argue that the specification disclose examples of "parenteral nonintracranial administration." However, while the specification discloses the genus of "parenteral administration", it does not disclose the subgeneric limitation of "nonintracranial". The specification does not disclose the negative limitation of "nonintracranial" and does not disclose the exclusion of intracranial from the genus of "parenteral administration" the intracranial to create a new subgenus of "parenteral nonintracranial administration" which is not disclosed in the specification. Appellants argue that the specification on page 3 discuss that intracranial administration was invasive and difficult, risky and required costly surgical procedure. However, the specification does not exclude intracranial from the parenteral administration method. The discussion of blood brain barrier does not support "parenteral nonintracranial administration" but rather supports "parenteral administration."

Claims 24-71 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of parenteral administration of the species of IGF-I, IGF-II, or a combination of both IGF-I and II for the treatment of locus ceruleus noradrenergic neurons ablation by 6-hydroxydopamine, does not reasonably provide the full scope of enablement for parenteral administration of IGF-I or IGF-II, for traumatic injury of the central nervous system (CNS) or spinal cord and treating stroke. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the reasons set forth in the past office actions.

Upon further consideration, the Declaration of Ishii filed 16 November 1998 is not found persuasive to overcome the enablement rejection.

Appellant argues that the post-filing date evidence clearly demonstrates the operativeness of the methods in a mammal as taught and claimed. However, appellant has failed to make a nexus from the model in the specification of using IGF-I and II for the treatment of locus ceruleus noradrenergic neurons ablation by 6-hydroxydopamine to treating stroke, traumatic injury to the CNS or the brain. Furthermore, the specification fails to teach the methods of administration of IGF which results in successful treatment an established model for diseases of stroke or traumatic injury to the brain or CNS.

Claims 24-71 are rejected under 35 U.S.C. 102(e) as being anticipated by Lewis

et al.(A1).

Appellants argue that Lewis et al. does not teach treatment of the brain by parenteral nonintracranial administration. Appellants argue that Lewis et al. teaches away from parenteral nonintracranial administration. However, Lewis et al. teach the method of parenteral administration of IGF-I or IGF-II with specific dosage ranges of 1ug/kg/day to 1 g/kg/day as well as ranges 0.01 mg/kg/day to 100mg/kg/day (column 10, lines 3-22). Lewis et al. teach different modes of parenteral administration of the IGF-1 and IGF-II, such as intravenous, subcutaneous, intramuscular and many more (column 9, lines 18-30) which are not intracranial. Furthermore, IGF I and II inherently cross the blood brain barrier. Lewis et al. teach solution of IGF acting across the blood-brain by making the polypeptide more lipophilic, by conjugating the polypeptide of interest to a molecule which is naturally transported across the barrier or by reducing the overall length of the polypeptide chain (column 3, lines 39-60; column 5, lines 10-26; column 6, lines 50-68; column 8, lines 45-55; and column 9).

Appellants argue that the Examples of Lewis are limited to either in vitro experiments or administration of modified IGF to rat models via a hole in the skull. However, Lewis et al. teach the method of parenteral administration of IGF-I or IGF-II with specific dosage ranges of 1ug/kg/day to 1 g/kg/day as well as ranges 0.01 mg/kg/day to 100mg/kg/day (column 10, lines 3-22). The Lewis et al. patent is not limited to the working example but also includes summary of the invention that includes the use of the peptides in parenteral administration of IGF-I and IGF-II (columns 9-10). Lewis et al. teach different modes of parenteral administration of the IGF-1 and IGF-II,

such as intravenous, subcutaneous, intramuscular and many more (column 9, lines 18-30) which are not intracranial.

Appellants argue that the scope of the IGF in appellant's claims does not include the "functional derivatives" of Lewis et al. However, the definition in the specification on page 5, lines 21-25 specifically recites that "IGF-I also encompasses ... IGF molecules with substantial sequence homology to human and animal IGF-I that bind to type I IGF receptors." Thus the IGF encompasses generically IGF molecules other than the species disclosed in the specification. Furthermore, the definition does not exclude fragments or derivatives.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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